Chronic hypersensitivity pneumonitis in patients diagnosed with idiopathic pulmonary fibrosis: a prospective case-cohort study

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Summary

Background The clinical features of idiopathic pulmonary fibrosis (IPF) and chronic hypersensitivity pneumonitis can be indistinguishable; the need to eliminate occult environmental factors known to cause pulmonary fibrosis in patients suspected to have IPF during diagnostic evaluation is evident. We aimed to investigate occult, putative causes in the environments of patients diagnosed with IPF using tests beyond those conventionally used.

Methods In this case-cohort study, 60 consecutive patients diagnosed with IPF on the basis of the 2000 American Thoracic Society (ATS) and the European Respiratory Society (ERS) criteria were prospectively followed up every 4 months for 6 years between Jan 1, 2004, and Dec 31, 2009. At each visit a uniformly applied questionnaire was administered to these 60 patients to identify occult antigen exposure known to cause hypersensitivity pneumonitis. Patients underwent specific IgG determination, bronchoalveolar lavage, bronchial challenge testing with suspected antigens, and re-review of histopathological features in existing and subsequently obtained surgical lung biopsy samples and from lung explants. Specimens obtained from suspected sources from the patient's environment were subjected to cultures in microbiology laboratory. These clinical data and discussions among pulmonologists and radiologists familiar with IPF were used to confirm the diagnosis in accordance with 2011 ATS, ERS, Japanese Respiratory Society, and Latin American Thoracic Association guidelines; 46 of the 60 patients had IPF according to the 2011 guidelines, and our analyses in this study were focused on these 46 patients.

Findings 20 of the 46 (43%, 95% CI 29–58) patients with IPF according to 2011 guidelines had a subsequent diagnosis of chronic hypersensitivity pneumonitis: nine patients had positive bronchial challenge testing (eight of whom were also IgG positive and six of these patients also had surgical lung biopsy showing a pattern consistent with chronic hypersensitivity pneumonitis); seven were IgG positive plus had histopathology on surgical lung biopsy that was consistent with hypersensitivity pneumonitis; one was IgG positive plus had greater than 20% lymphocytes in bronchoalveolar lavage fluid; and three had findings on surgical lung biopsy that were consistent with subacute hypersensitivity pneumonitis (and IgG positive). Altogether, 29 of 46 patients diagnosed with IPF who had met the 2011 criteria had lung tissue available for histopathology (surgical lung biopsy in 28 patients and explanted lung in two patients, one of whom also had surgical biopsy) during the study period, and 16 of the 20 patients with chronic hypersensitivity pneumonitis had histopathological features on surgical lung biopsy that were consistent with this diagnosis. 26 of the 46 patients remained with a diagnosis of IPF.

Interpretation Almost half of patients diagnosed with IPF on the basis of 2011 criteria were subsequently diagnosed with chronic hypersensitivity pneumonitis, and most of these cases were attributed to exposure of occult avian antigens from commonly used feather bedding. Our results reflect findings in one centre with recognised expertise in chronic hypersensitivity pneumonitis, and further research and studies at other centres are warranted.

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Introduction

Idiopathic pulmonary fibrosis (IPF) is a distinct fibrotic lung disease manifesting in adults, and its diagnosis and clinical features have been well established in evidence-based guidelines.[1] The annual incidence in the USA[2] between 1996 and 2000 ranged from 1·2 to 76·4 per 100 000 person-years using narrow or broad criteria and is 7·4 per 100 000 person-years in the UK.[3] The prognosis of IPF is very poor, with mean survival varying from 3–5 years.[1,4] The 2011 guidelines[1] for diagnosis and management of IPF emphasise the need to exclude all known causes associated with interstitial lung diseases or pulmonary fibrosis; however, the burden of this elimination and the clinical index of suspicion for diagnosis of hypersensitivity pneumonitis rests on the individual clinician and their investigation. In this respect, environmental factors at home and at work are very important, not only to aid in the correct diagnosis but also to recommend avoidance of further exposure to the identified antigen or factor because this is prudent to the management of patients with interstitial lung diseases or pulmonary fibrosis. To pursue such preventive measures, proactive efforts are needed to identify potential environmental factors that might cause pulmonary fibrosis.

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In the appropriate clinical setting, the presence of radiological or histopathological features of usual interstitial pneumonia is a diagnostic criterion for IPF.[4] However, this characteristic pattern of usual interstitial pneumonia is not pathognomonic of IPF because it has been observed in patients with chronic hypersensitivity pneumonitis, collagen vascular diseases, asbestosis, and other contexts.[5–8] Thus, some patients diagnosed with IPF might in fact have chronic hypersensitivity pneumonitis and exposure to the antigen might have been occult or forgotten.[9,10] Exposure to avian antigens by contact with birds is a well recognised common cause of hypersensitivity pneumonitis (so-called bird fancier's lung), but exposure can also occur in circumstances other than by direct contact with live birds. One such situation is exposure through feather bedding use, which in susceptible individuals can lead to development of the hypersensitivity pneumonitis named feather duvet lung.[11–14]

We aimed to test the hypothesis that some patients diagnosed with IPF on the basis of the 2011 guidelines actually have chronic hypersensitivity pneumonitis caused by exposure to an occult antigen or antigens known to cause hypersensitivity pneumonitis. We believe that inconspicuous but persistent exposure to such antigens might provoke asymptomatic lung disease that goes unnoticed until it has progressed to stages of pulmonary fibrosis with features of usual interstitial pneumonia and is eventually misdiagnosed or labelled as IPF. Furthermore, such occult factors can only be identified with meticulous protocolised clinical, immunological, and pathological study to allow accurate diagnosis and appropriate treatment intervention.

Methods

Study population

In this case-cohort study, from Jan 1, 2004, to Dec 31, 2009, 305 consecutive and previously unreported outpatients were prospectively evaluated within the interstitial lung diseases programme of Hospital Universitari Vall d'Hebron (Barcelona, Catalonia, Spain) in accordance with a research protocol approved by the centre's ethics committee. All patients seen in the interstitial lung diseases clinic during the study period and diagnosed with IPF on the basis of international guidelines published in 2000 from the American Thoracic Society (ATS) and the European Respiratory Society (ERS)[4,15] were included. Patients with IPF referred to the lung transplantation programme during this period were not included, since they were not evaluated further in our interstitial lung diseases programme. Patients referred for lung transplantation were younger than 65 years with forced vital capacity (FVC) less than 50% and diffusing capacity of the lung for carbon monoxide (DLCO) less than 30% of predicted values. During the study period, only five patients were referred to the lung transplant programme and were therefore not included in the study; they were listed for lung transplantation.

See Online for appendix

60 consecutive patients who met the diagnostic criteria for IPF according to the 2000 guidelines and who had no other potential causes of interstitial lung disease, including exposure to birds (fewer than nine birds per year; the minimum exposure value found in chronic hypersensitivity pneumonitis),[11] were included in the study. 40 patients were living in our region and 20 patients (33%) were referred from other areas for further management to our programme. Of these 60 patients, the diagnosis in 41 patients who initially had not undergone surgical lung biopsy was based on clinical criteria and high-resolution CT findings of a usual interstitial pneumonia pattern,[1] provided that transbronchial biopsy and bronchoalveolar lavage findings yielded no indicators to support an alternative diagnosis.[4] Patients with ground glass opacities involving more than 5% of the lung on high-resolution CT or lymphocyte count greater than 30% in bronchoalveolar lavage specimens[16] were excluded. 19 patients diagnosed with IPF on the basis of clinical and high-resolution CT criteria had also undergone surgical lung biopsy, initially interpreted as usual interstitial pneumonia. However, nine of these 19 patients did not fulfil the criteria for the new (2011) ATS, ERS, Japanese Respiratory Society, and Latin American Thoracic Association diagnostic criteria for IPF[1] because the histopathological features were not consistent with the usual interstitial pneumonia pattern. Additionally, multidisciplinary consensus discussions among the three interstitial lung disease clinicians (FM, AV, and GR) and the radiologist (SP) led to exclusion of an additional five patients on the basis of the 2011 radiological criteria for usual interstitial pneumonia pattern (one of them had surgical lung biopsy showing usual interstitial pneumonia). Thus, 46 patients met the newly defined 2011 criteria for IPF (nine of them having surgical lung biopsy showing a usual interstitial pneumonia pattern) and the data analyses in this study were focused on these 46 patients. The validity of the 2011 IPF diagnosis was further supported in 26 of these 46 patients who had been accepted and enrolled in clinical trials investigating antifibrotic drugs for IPF, since only patients with well defined disease were accepted for such studies and the diagnosis was confirmed by an independent panel of experts.

Procedures

At visits scheduled every 4 months, the 60 consecutive patients who initially received a diagnosis of IPF based on 2000 guidelines were re-questioned by the same senior faculty investigator (FM), using our standardised antigen exposure questionnaire (appendix) designed to identify even minimal antigenic sources, in particular exposure to feather bedding (duvets or pillows) for at least 1 year before the initial evaluation. Previous data, including surgical lung biopsy findings, were reassessed by two masked pathologists (M-ÁM and TVC). The patterns of interstitial lung diseases, pulmonary fibrosis, and usual interstitial pneumonia on high-resolution CT scans of the patients were independently interpreted by

an external clinical expert (GR) on interstitial lung disease and IPF and a chest radiologist (SP); the pattern was not typical of usual interstitial pneumonia pattern in five patients, who were therefore excluded from the study. The decision to undertake additional tests during reassessment was made according to a previously reported strategy and criteria used for diagnosis of hypersensitivity pneumonitis.[11]

In the 46 patients who had met the 2011 criteria for IPF, the following tests that are not generally suggested or recommended by 2011 guidelines[1] for routine evaluation of patients suspected to have IPF were also done: specific serum IgG determination in 46 (100%) of 46 patients, bronchoalveolar lavage cellular analysis in 44 (96%) patients (although the 2011 guidelines did not recommend this procedure to be done routinely for patients suspected to have IPF, the 2000 guidelines had recommended this analysis in patients not subjected to surgical lung biopsy), bronchial challenge testing in ten (22%) patients, and culture of suspected material from patients' environment for fungi in 11 (24%) patients. Specific serum IgG testing (appendix) was done only once at baseline during the initial evaluation with goose, pigeon, parrot, parakeet, canary, and hen sera, *Aspergillus, Penicillium, Mucor,* and *Rhizopus* extracts, and extracts prepared from the feathers (duvet or pillow) to which patients were exposed. The methods used to prepare antigen extracts and determine specific IgG antibodies were described in a previous study[11] and are included in the appendix. Bronchial challenge testing was done with the suspected antigen in patients with sufficiently preserved lung function (FVC >50%, DLCO >40%), as described previously[11] (appendix). Bronchoalveolar lavage was done in accordance with European Respiratory Society standards,[17] and transbronchial biopsy was done as reported elsewhere;[18] the decision to subject patients to surgical lung biopsy versus transbronchial biopsy or both was a clinical one and based on the present recommendations[4] and patients' willingness and tolerance to procedures.

On the basis of the questionnaire results or positive specific IgG testing, bronchoalveolar lavage results, and negative bronchial challenge testing (if done), surgical lung biopsy was done in an additional 19 patients during follow-up, and explanted native lungs were examined in two patients who underwent transplantation, one of whom had undergone surgical lung biopsy previously. The histopathological features of the nine surgical biopsy specimens obtained at the time of original diagnosis, 19 additional surgical biopsy specimens obtained during the study, and two explanted lungs (one of whom had surgical lung biopsy at the time of the diagnosis of IPF), hence a total of 29 lung tissues (biopsy specimens), were re-examined by the study pathologists (M-ÁM and TVC) from two different centres masked to the data for environmental factors, IgG values, and bronchial challenge testing results. The high-resolution CT images of the chest were interpreted as usual interstitial pneumonia pattern by two clinical experts on interstitial lung diseases and IPF at the centre where patients were directly evaluated (FM and AV) and independently by a consensus reached by discussion among one senior interstitial lung disease and IPF expert clinician (GR) and an expert chest radiologist (SP) at a recognised centre with expertise in interstitial lung diseases and IPF. The interpretation of all the high-resolution CT images was based on review of the CT patterns by GR and SP.

All surviving patients were followed up for at least 18 months up to June, 2011, when the study concluded. Panel 1 shows diagnostic criteria for hypersensitivity pneumonitis. A diagnosis of chronic hypersensitivity pneumonitis was made if the non-invasive criteria were satisfied or a histological pattern of hypersensitivity pneumonitis was identified at biopsy.[9]

Statistical analysis

Results were expressed as the median and IQR for quantitative variables and as frequencies and percentages for qualitative variables, unless otherwise stated. Between-group differences were analysed with the Mann-Whitney test for continuous data. The χ^2 test

***Panel 1*: Diagnostic criteria for chronic hypersensitivity pneumonitis**

Chronic hypersensitivity pneumonitis can be diagnosed in patients with clinical and high-resolution CT findings of usual interstitial pneumonia or idiopathic pulmonary fibrosis meeting any one of the following three criteria:

- Positive bronchial challenge testing (this criterion is reinforced by often coinciding with positivity of specific IgG).
- Specific IgG positivity and surgical lung biopsy sample compatible with hypersensitivity pneumonitis or greater than 20% lymphocytes in bronchoalveolar lavage specimen (>20% lymphocytes is seen in 85% of patients with chronic hypersensitivity pneumonitis;[11] see Discussion).
- Surgical lung biopsy sample or explanted lung showing histopathological features or characteristics of subacute hypersensitivity pneumonitis (see below).

Pathological criteria for diagnosis of subacute and chronic hypersensitivity pneumonitis (surgical lung biopsy):

- Subacute hypersensitivity pneumonitis: cellular bronchiolitis or centrilobular scarring, plus interstitial lymphoplasmacytic infiltrate, and poorly formed non-necrotising granulomas.
- Consistent with chronic hypersensitivity pneumonitis: interstitial fibrosis with a pattern of non-specific interstitial pneumonia, organising pneumonia or usual interstitial pneumonia, and features atypical for usual interstitial pneumonia, including prominent peribronchiolar metaplasia, marked interstitial lymphoplasmacytic infiltrates, lymphoid aggregates without germinal centres, relatively prominent organising pneumonia, granulomas, and constrictive or obliterative bronchiolitis.[7,17] On the basis of the most recently published guidelines,[1] prominent centrilobular and bronchiolocentric lesions were judged atypical for idiopathic pulmonary fibrosis and favoured a diagnosis of chronic hypersensitivity pneumonitis.

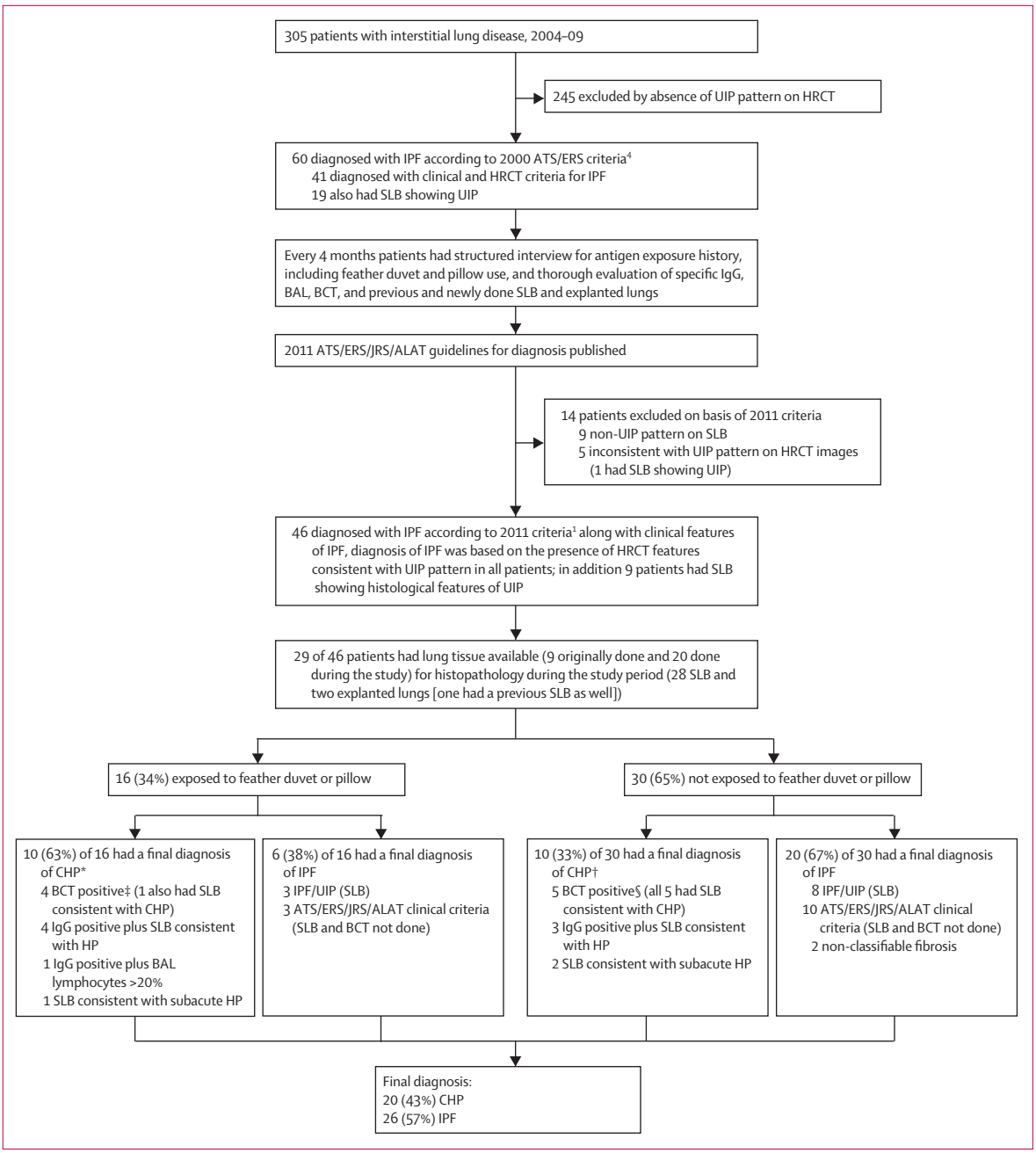

Figure: **Patients diagnosed with IPF according to criteria published in 2000 and 2011, and subsequently diagnosed with chronic hypersensitivity pneumonitis**
Final diagnosis in 46 patients originally diagnosed with IPF according to 2011 guidelines.[1] IPF=idiopathic pulmonary fibrosis. ATS=American Thoracic Society. ERS=European Respiratory Society. UIP=usual interstitial pneumonia. SLB=surgical lung biopsy. HRCT=high-resolution CT. BAL=bronchoalveolar lavage. BCT=bronchial challenge testing. JRS=Japanese Respiratory Society. ALAT=Latin American Thoracic Association. CHP=chronic hypersensitivity pneumonitis. HP=hypersensitivity pneumonitis. *Five patients exposed to feather bedding or its fungal contaminants, five patients exposed to feathers. †Three patients exposed to birds (with a total historical exposure to fewer than nine birds per year [an exposure to one bird during 9 years or to nine birds during 1 year]);[9] four patients exposed to sources of fungal exposure other than feather bedding; one patient exposed to isocyanate inhalation; and for two patients no putative exposure to an antigen was identified. ‡BCT positive in two patients, two to birds, one to feathers and one to *Penicillium*. §BCT positive in two patients to *Penicillium*, one to *Aspergillus*, one to isocyanate, and one to birds; altogether, 16 patients had histopathological features of hypersensitivity pneumonitis on SLB (six also BCT positive).

and the Fisher exact test were used to compare the nominal variables. 95% CIs were calculated to describe uncertainty of the estimates. SPSS 17.0 for Windows was used for statistical analyses.

Role of the funding source

The sponsors of the study did not have any role in the design, data collection, analysis, and interpretation, nor in writing of the report. FM had full access to all data in the

study and takes responsibility for the integrity of the data and the accuracy of the data analysis; GR also had access to all clinical data including high-resolution CT scans; both FM and GR had final responsibility of approval to submit for publication.

Results

Of the 46 patients who met the 2011 criteria for IPF, 16 (34%) had been exposed to feather duvets or pillows and ten (63%) of these 16 patients were diagnosed with chronic hypersensitivity pneumonitis. Among the 30 of 46 patients who did not have a history of exposure to feather duvets or pillows, ten (33%) were diagnosed with chronic hypersensitivity pneumonitis (figure). Altogether, 20 (43%, 95% CI 29–58) patients were identified as having chronic hypersensitivity pneumonitis during the study: nine patients had positive bronchial challenge testing (eight of whom were also IgG positive and six of these also had surgical lung biopsy showing a pattern consistent with chronic hypersensitivity pneumonitis); seven were IgG positive plus had a surgical lung biopsy consistent with hypersensitivity pneumonitis; one was IgG positive plus had greater than 20% lymphocytes in bronchoalveolar lavage fluid; and three had surgical lung biopsy findings characteristic of subacute hypersensitivity pneumonitis (and IgG positive; panel 1, appendix). Altogether, 16 of the 20 patients with chronic hypersensitivity pneumonitis had histopathological features on surgical lung biopsy that were consistent with this diagnosis.

Among the 46 patients who had serum determination of specific IgG, 29 (63%) were positive (five to avian antigens, 14 to fungi, nine to both, one to isocyanates and fungi) and three patients (all from the IPF group) had indeterminate results.

Demographic and clinical characteristics did not differ significantly between the 26 of 46 patients who remained with a diagnosis of IPF and the 20 patients with diagnosis of chronic hypersensitivity pneumonitis, except for DLCO, which was 12% lower in patients with IPF (95% CI −21·2 to −3·1; p=0·010), and the number of surgical lung biopsies done, which was 30% lower in patients with IPF than in those with chronic hypersensitivity pneumonitis (95% CI −56·0 to −4·0; p=0·037; table).

The final diagnosis was made using lung tissue obtained by surgical lung biopsy or explants in 29 of the 46 patients reviewed during the study period. Among the 26 patients whose diagnosis remained as IPF after further evaluation in this study, 11 had surgical lung biopsy showing usual interstitial pneumonia; samples from two patients diagnosed with IPF who had UIP pattern on high-resolution CT were subsequently thought to have histological features of non-classifiable interstitial pneumonia. 16 of the 20 patients subsequently diagnosed with chronic hypersensitivity pneumonitis had evidence of this diagnosis on surgical lung biopsy. Thus the percentage of patients with a subsequent diagnosis of chronic hypersensitivity pneumonitis exclusively among patients who had lung tissue available for histopathology was 55% (ie, 16/29).

	All patients	Final diagnosis		Difference (95% CI)
		True IPF	Chronic hypersensitivity pneumonitis	
n	46	26	20	
Age (years)	67 (61–70)	67 (62–72)	63 (59–70)	4·0 (−1·4 to 7·2)
Men	32/46 (70%)	17/26 (65%)	15/20 (75%)	−9·6 (−35·9 to 16·7)
Smokers*	22/46 (48%)	12/26 (46%)	10/20 (50%)	−3·8 (−32·9 to 25·3)
Exposure to feather duvet or pillow(s), or both	16/46 (35%)	6/26 (23%)	10/20 (50%)	−26·9 (−54·2 to 0·3)
Disease duration (years)†	4·0 (2·0-7·0)	5·5 (2·8-9·5)	3·0 (1·5-6·0)	2·5 (−0·6 to 5·5)
Velcro crackles	21/46 (46%)	11/26 (42%)	10/20 (50%)	−7·7 (−36·7 to 21·3)
Clubbing	11/46 (24%)	6/26 (23%)	5/20 (25%)	−1·9 (−26·9 to 23·0)
Raised LDH	31/40 (76%)	16/22 (73%)	15/18 (83%)	−10·6 (−35·9 to 14·7)
ESR >20 mm/h	19/37 (51%)	11/21 (52%)	8/16 (50%)	2·4 (−30·1 to 34·9)
FVC (%) of predicted	70·51	67·34	74·85	−7·5 (−16·3 to 1·3)
TLC (%) of predicted	74·72	75·50	74·08	−1·4 (−9·7 to 12·5)
DLCO (%) of predicted	50·57	45·23	57·38	−12·2 (−21·2 to −3·1)
BAL lymphocytes 15–20%	5	3	2	..
BAL lymphocytes >20%	3	0	3	..
IPF clinical trial participants	26/46 (57%)	16/26 (62%)	10/20 (50%)	11·5 (−17·3 to 40·3)
Surgical lung biopsy done	29‡/46 (63%)	13/26 (50%)	16‡/20 (80%)	−30·0 (−56·0 to −4·0)

Data are median (IQR), n, or n/N (%). IPF=idiopathic pulmonary fibrosis. LDH=lactate dehydrogenase. ESR=erythrocyte sedimentation rate. FVC=forced vital capacity. TLC=total lung capacity. DLCO=diffusing capacity of the lung for carbon monoxide. BAL=bronchoalveolar lavage. *Current smokers and ex-smokers. †Time from onset of symptoms to 2010. ‡Surgical lung biopsy plus one explant.

Table: **Demographic and clinical data for 46 patients diagnosed with IPF on the basis of 2011 published guidelines[1]**

16 (34%) of the 46 patients with IPF on the basis of 2011 guidelines had usually slept with feather duvets or pillows, or both, in the years preceding their diagnosis. Moreover, in half of them (eight of 16), the onset of symptoms coincided with acquisition of these feather products. Among the 16 patients using feather bedding, ten (63%) had a final diagnosis of chronic hypersensitivity pneumonitis versus ten (33%) of 30 patients who did not use the feather bedding (p=0·10; figure). The offending agent in the 20 patients with a final diagnosis of chronic hypersensitivity pneumonitis was feather bedding in ten (feathers in five, feathers and fungi in five), fungi from other sources in four, birds in three (exposure to fewer than nine birds per year), isocyanate in one, and unknown antigen in two patients (both had undergone surgical lung biopsy that revealed subacute hypersensitivity pneumonitis).

Median length of follow up was 48 (IQR 24–84) months. During follow-up, seven patients died and two received lung transplants (nine [20%] of 46 patients with IPF according to 2011 criteria). Only two of these nine patients were from the chronic hypersensitivity pneumonitis group (two [10%] of 20 patients) versus seven (27%) of 26 patients diagnosed with IPF according to 2011 criteria.

Discussion

In this prospective observational study of consecutive patients with well defined IPF in accordance with the current 2011 criteria for diagnosis of IPF,[1] a third of patients on further history elicitation and leading questionnaires had occult exposure to feather duvets or pillows and two-thirds of those patients exposed were diagnosed with chronic hypersensitivity pneumonitis (panel 2). Altogether, almost half of patients diagnosed with IPF on the basis of the 2011 criteria had a final diagnosis of chronic hypersensitivity pneumonitis. On the basis of serum specific IgG, two-thirds of patients with IPF according to 2011 guidelines had been exposed to antigens known to cause hypersensitivity pneumonitis. The cause of the disease originally thought to be IPF in most of these cases was exposure to occult avian antigens including exposure to feather duvets or feather pillows. This almost unrecognised cause of hypersensitivity pneumonitis (using blankets or pillows stuffed with feathers for comfort) might be responsible for disease in many patients labelled as having IPF.

Our findings emphasise and support the recommendations made in the 2011 guidelines to exclude environmental causes in patients suspected to have IPF. Although the 2011 evidence-based guidelines for diagnosis of IPF do state the importance of exclusion of known causes and environmental factors that can cause pulmonary fibrosis, there are no validated questionnaires that could be recommended to exclude such causes. The results of this study emphasise the need for a clinician evaluating patients with suspected IPF to consider such a questionnaire and to be prudent and diligent in exploring potential and occult factors in the domestic environment that might have caused a fibrotic response in the lung that could otherwise be misdiagnosed as IPF.[20] Since the cause of chronic hypersensitivity pneumonitis in the subgroup of patients seen at our centre was thought to have been occult exposure to avian antigens with the use of feather duvets and pillows, our results support the inclusion of a questionnaire regarding such occult exposure; when this exposure is noted, further diagnostic interventions to rule out hypersensitivity pneumonitis would be appropriate. We recognise that the use of feather pillows, duvets, and blankets in some parts of the world might be quite common, and thus many patients with manifestations of pulmonary fibrosis and clinical features of IPF may also have a history of exposure, and might need further investigation to avoid misdiagnosis.

The clinical differentiation between IPF and chronic hypersensitivity pneumonitis can be very difficult. Chronic hypersensitivity pneumonitis and IPF can present with similar clinical, radiological, and pathological features.[7,21] The results of this study support the need for a very careful and thorough elicitation of an exposure history, and when this history suggests exposure to an occult antigen in the patient's environment, a comprehensive diagnostic protocol similar to the one undertaken in the present study might help to ascertain the diagnosis of chronic hypersensitivity pneumonitis or IPF. We are hopeful that an exhaustive patient history, detection of specific IgG, bronchoalveolar lavage lymphocytosis, cultures of fungi from suspected material in the domestic environment, bronchial challenge testing with suspected material and fungi, and re-evaluation of the available surgical lung biopsy sample with multidisciplinary discussion between pathologists and experts in regional centres will be adequate in almost all cases. Surgical lung biopsy would be considered only if this sample had not already been obtained as a diagnostic intervention and the other diagnostic tests for chronic hypersensitivity pneumonitis are not conclusive. Thus we do not feel that every patient with a pattern on high-resolution CT that is consistent with usual interstitial pneumonia and an exposure to feather pillows or duvets must undergo surgical lung biopsy to eliminate chronic hypersensitivity pneumonitis.

We note our patient population was selected and that our findings are limited to a cohort of patients living in our area, a third of whom were referred from other centres for further management in our interstitial lung diseases programme. However, our study does reflect a consecutive series of patients who were diagnosed with IPF based on the 2011 established criteria during the study period, and our results raise the important concern

Panel 2: Research in context

Systematic review

We searched PubMed on June 23, 2013, for the search terms "IPF and Feather Duvet" and were not able to find any pertinent references. We also searched for "IPF and environmental fungi" and only two publications were disclosed. One described a case of chronic hypersensitivity pneumonitis after exposure to *Cladosporium* that was misdiagnosed as idiopathic pulmonary fibrosis (IPF).[18] The second publication described two cases of chronic summer-type hypersensitivity pneumonitis misdiagnosed as idiopathic interstitial pneumonia.[19]

Interpretation

Our study appears to be the first series of patients with well defined IPF who were exposed to feather duvets or environmental fungi and subsequently confirmed to have chronic hypersensitivity pneumonitis. This finding emphasises the need to elicit a very thorough history of exposures to occult or subtle agents linked to manifestation of pulmonary fibrosis, to raise the probability of chronic hypersensitivity pneumonitis in differential diagnosis if such an occult exposure history is elicited, and pursue the diagnosis of chronic hypersensitivity pneumonitis by further diagnostic interventions in such patients who might be otherwise diagnosed with IPF. Our data should be interpreted with awareness that they reflect findings from a single centre with recognised expertise in chronic hypersensitivity pneumonitis and that further research and studies at other centres are warranted.

that an appreciable percentage of this patient population might have chronic hypersensitivity pneumonitis secondary to subtle, domestic environmental factors.

Since the current criteria for usual interstitial pneumonia pattern require the presence of honeycombing on high-resolution CT and the diagnosis of IPF requires the presence of an usual interstitial pneumonia pattern, our results also raise the possibility that some patients diagnosed with IPF might simply be manifesting an end-stage pathological process of chronic hypersensitivity pneumonitis, initiated and perpetuated by subtle and occult environmental factors. Thus, there are potential limitations and pitfalls in making the diagnosis of IPF if the clinician does not elicit a sufficiently thorough medical history, does not assess the patient with leading questionnaires inclusive of environmental factors to reveal exposures that might be otherwise occult or not disclosed by the patient, and if the clinician's index of suspicion is not high to pursue the diagnosis of chronic hypersensitivity pneumonitis.

The relatively high percentage of diagnosis of chronic hypersensitivity pneumonitis in this series of patients who met established international criteria for IPF[1,4] might be explained in part by a few possible factors. First, the 2011 guidelines allow a patient to be diagnosed with IPF on the assumption that the clinician eliminated potential environmental factors known to be associated with interstitial lung diseases or pulmonary fibrosis and on the basis of consistent clinical features inclusive of characteristic features of usual interstitial pneumonia pattern on high-resolution CT alone. The guidelines acknowledge that there are no validated questionnaires to screen for attributable environmental exposures and do not discuss or comment on systematic determination of specific IgG antibodies, obligatory bronchoalveolar lavage cellular analyses to consider chronic hypersensitivity pneumonitis based on bronchoalveolar lavage lymphocytosis, or bronchial challenge in specific IgG-positive patients or those with a positive culture of fungi or spores from environmental sources, as was done in our study. Second, the diagnosis in our study was established after exhaustive, repeated questioning about the patient's background of exposure to agents causing hypersensitivity pneumonitis (administered directly by the same senior faculty investigator in all patients) and accompanied with the battery of tests outlined above. Third, surgical lung biopsy was obtained in a higher than usual percentage of patients mainly because of our higher index of suspicion for chronic hypersensitivity pneumonitis during the study period and availability of tissue from explanted lungs in transplant recipients. A fourth, potential contributing factor is our own extensive experience in the management of interstitial lung diseases and specifically chronic hypersensitivity pneumonitis including occupational and environmental respiratory diseases at our centres.[11,22–24] Finally, we used bronchial challenge to support the diagnosis of hypersensitivity pneumonitis in a subset of patients, acknowledging that this procedure is still a research method that needs validation.[11,25,26] Indeed, bronchial challenge testing is only done in a few centres with expertise and familiarity with such testing. At our centre, the positive predictive value of bronchial challenge testing for a diagnosis of hypersensitivity pneumonitis is 94% and a negative predictive value of 71% (data presented at ERS Vienna Congress;[27] and unpublished data). The concepts in the pathogenesis of chronic hypersensitivity pneumonitis and IPF are similar: both diseases are a consequence of recurrent insults or injury to the lung. In chronic hypersensitivity pneumonitis, the initiating and perpetuating trigger if either known and identified or occult can lead to clinical and radiological features of IPF or usual interstitial pneumonia. In a subpopulation known to have chronic hypersensitivity pneumonitis by radiological or histopathological study of the surgical lung biopsy sample, the triggers might never be discovered and could present as or mimic features of IPF; thus the overall outcomes and clinical management might be similar in patients with advanced stages of pulmonary fibrosis associated with chronic hypersensitivity pneumonitis and IPF.

A striking feature of the patients thought to have IPF according to 2011 guidelines and later diagnosed in this study with chronic hypersensitivity pneumonitis is that most patients did not have previous symptoms of acute or subacute pneumonitis. This might be because chronic hypersensitivity pneumonitis resembling IPF is a consequence of minimal but persistent and recurrent inhalation of the offending antigen, which gradually leads to a characteristic clinical picture of fibrosis without previous acute or subacute symptoms. This hypothesis is in keeping with the widely accepted concept of abnormal wound healing in the pathogenesis of IPF.[28] In the case of chronic hypersensitivity pneumonitis associated with exposure to feather bedding, the chronic insult would be avian antigen present in feathers and feather dust, or fungi contaminating the feathers. In some cases, the antigen might be inhaled in a way that the patient might not account for, for example in trombone or saxophone players whose instruments might be contaminated by hidden spores or fungi.[29,30]

The hypothesis of recurrent, subtle exposure is further supported by observations from Ohtani and colleagues.[9] In the hypersensitivity pneumonitis type, which is typically seen in pigeon keepers who are subjected to high antigenic loads, patients show recurrent symptoms, a small percentage have clubbing (7%), fever (33%), positive specific IgG testing to dropping extracts (86%), and increased bronchoalveolar lavage lymphocytes (70%). The second group is a more insidious type of hypersensitivity pneumonitis, caused by low but persistent levels of antigen in which percentages of the above mentioned characteristics are 53%, 0%, 35%, and 23%, respectively. These latter values are more similar to

the ones obtained in our patients finally diagnosed with chronic hypersensitivity pneumonitis (25%, 0%, 50%/70% [ELISA-positive to avian serum or fungi extracts], and 16% [bronchoalveolar lavage lymphocytes higher than 20%], respectively). Furthermore, eight of the 12 patients in Ohtani's series with the insidious form had pathological features of usual interstitial pneumonia, described as predominantly centrilobular and perilobular, and with lymphoid hyperplasia, intrabronchiolar organising processes, and diffuse interstitial infiltration of inflammatory cells. These features are now recognised as characteristic of hypersensitivity pneumonitis.[31]

Since 63% of patients thought to have IPF in our study who used feather bedding were ultimately diagnosed with chronic hypersensitivity pneumonitis, our findings support the inclusions of feather bedding, pillows, and blankets to the list of exposures known to be associated with interstitial lung diseases, IPF, and hypersensitivity pneumonitis. Our observations emphasise the need to take a very thorough history during initial and follow-up clinical visits, paying close attention to subtle exposure history to environmental factors such as feathers, moulds (as well as water leaks, moisture collections on walls, corners, etc), hot tubs, neglected ventilation systems, and heat sources. At the start of our study we strove to be especially discerning when applying the consensus IPF criteria[4] and eliminating potential diagnosis of chronic hypersensitivity pneumonitis. The diagnostic accuracy is further enhanced by evaluation by experts in an experienced centre for interstitial lung diseases, with multidisciplinary discussions, as recommended by the 2011 guidelines (as was done in our study). The apparent increased incidence of IPF documented in recent years in the general population[3] might in part be due to an assumed diagnosis of IPF, with a substantial proportion of such patients having occult chronic hypersensitivity pneumonitis instead.

We acknowledge several potential limitations of our study. Our study took place at a single centre, with a fairly small study population. We had known expertise in management of chronic and non-chronic hypersensitivity pneumonitis, and there might have been an apparent selection bias based on the practice of referral to our interstitial lung disease clinics or programme, since patients with IPF referred directly to our lung transplantation programme during the same study period (2004–09) were not included. Furthermore, we acknowledge the known challenges in diagnosis of hypersensitivity pneumonitis, since in general this diagnosis is based on elicitation of history of exposure to an attributable antigen, constellation of clinical signs and symptoms, and is a clinical diagnosis. In our study, we established the diagnosis of chronic hypersensitivity pneumonitis using prespecified criteria, based on previously published criteria;[11] in one patient, the diagnosis was based on positive specific IgG testing plus bronchoalveolar lavage lymphocytosis greater than 20%. Application of this latter criterion was based on evidence that the percentage of lymphocytes in bronchoalveolar lavage samples of healthy non-smokers was 5–15%[17] and also that 85% of patients with chronic bird fancier's lung have a percentage greater than 20%.[9] Additionally, bronchoalveolar lavage lymphocytosis in two series of IPF or usual interstitial pneumonia was greater than 15% only in 4% of patients[16] and lymphocytosis greater than 20% was only documented in 16% of patients.[32] Our diagnosis of chronic hypersensitivity pneumonitis was made by bronchial challenge in a subset of patients (nine of 20)—a procedure that is regarded as a research aid and done in only experienced centres familiar with such procedures. However, such research aids have been used in other studies to establish diagnosis in patients with hypersensitivity pneumonitis and berylliosis.[25,33] Despite elimination of the nine patients whose diagnosis of hypersensitivity pneumonitis was made on the basis of bronchial challenge testing and the exposure history elicited, the proportion of patients diagnosed with subsequent histopathology consistent with chronic hypersensitivity pneumonitis (16 of the 20 patients had features on a surgical lung biopsy sample of chronic hypersensitivity pneumonitis) in this cohort of patients with IPF according to 2011 criteria, is so significant that it should alert the clinician to be prudent in exploration of possible environmental exposures such as occult avian antigens linked with pulmonary fibrosis, and in appropriate cases refer to regional centres with recognised expertise in management of interstitial lung diseases including hypersensitivity pneumonitis for further diagnostic interventions. We also note that the demographic data for patients with IPF according to 2011 criteria who were subjected to further investigations to diagnose chronic hypersensitivity pneumonitis in our study were similar to those for the well defined patient populations with IPF enrolled in clinical trials.[34–41] And, as noted, half of these patients had met the rigid inclusion criteria for IPF clinical trials and their clinical data had been reviewed by an independent panel of IPF experts. Thus, this patient population with IPF according to 2011 criteria, despite the relatively small number, do represent the patient population diagnosed with IPF in accordance with current guidelines.[1]

In conclusion, more than 40% of patients in this study who met the diagnostic criteria for IPF according to the 2011 evidence-based guidelines for diagnosis and management actually had chronic hypersensitivity pneumonitis and this raises the probability that a proportion of patients diagnosed with IPF on the basis of current criteria[1] might actually have chronic hypersensitivity pneumonitis. In individuals presenting with interstitial lung disease, history elicitation should include detailed questions regarding domestic environmental factors including overt exposure to birds at home or in the workplace or frequent visits to homes or sites infested with birds or where birds are kept, besides eliciting history of otherwise subtle exposures to avian antigens

such as bird droppings (on window sills, patios, etc), bird nests in attics, roofs, close proximity and regular exposure to birdfeeders (eg, on patio), sleeping with feather duvets and pillows, fungi, and unkempt ventilation systems. It should be recognised that the relatively high percentage of chronic hypersensitivity pneumonitis observed in our study might be inherent to the patients from our region who might be genetically predisposed to manifest hypersensitivity pneumonitis, and thus the results from our study might not be reproduced in patients from other regions in further studies and other settings. Nevertheless, further studies from other regions and referral centres are warranted to investigate the possibility of chronic hypersensitivity pneumonitis caused by otherwise subtle, similar, or other environmental factors as an occult diagnosis and its prevalence in patients suspected to have IPF. Regardless, we hope that the results of our study will promote discussion and hopefully initiate the development of new or an update of existing guidelines that are clearer than existing criteria, to assist clinicians in the diagnosis and evaluation of patients presenting with interstitial lung disease and suspected to have idiopathic interstitial pneumonia or IPF to rule out the possibility of chronic hypersensitivity pneumonitis.

Contributors

FM contributed to the design of the study, visited and recruited the patients, and was responsible for writing the report. AV visited and recruited the patients, participated in writing the report, and contributed to designing the database. M-ÁM was responsible for immunopathological testing, studied and revised all the surgical biopsies, and participated in editing and revising the report. XM was responsible for pulmonary function and bronchial challenge testing and participated in revising the report. TVC reviewed all the surgical biopsies and participated in editing and revising of the report. SP reviewed the high-resolution CT images and discussed them with GR. M-JC was responsible for the immunological testing. GR contributed to the evaluation of cases, interpreted the high-resolution CT images, and discussed the CT findings with SP and was directly responsible for writing the report after review of all the data with FM and AV.

Conflicts of interest

We declare that we have no conflicts of interest.

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